Cell Division

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Prokaryotic Cell Division

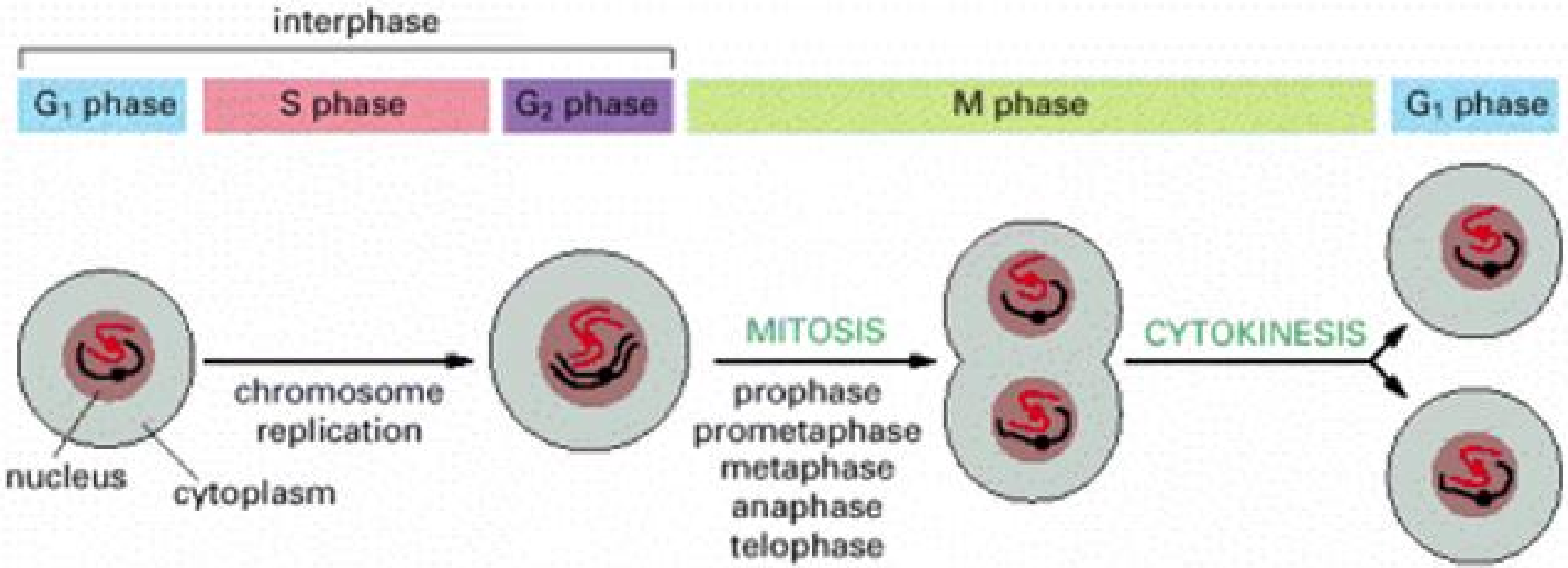
- Bacterial cell division happens through binary fission or through budding.
- The divisone is a protein complex in bacteria that is responsible for cell division, constriction of inner and outer membranes during division, and remodeling of the peptidoglycan cell wall at the division site.
- A tubulin-like protein, FtsZ plays a critical role in formation of a contractile ring for the cell division.

Eukaryotic Cell Division

- Mitosis is a form of eukaryotic cell division that produces two daughter cells with the same genetic component as the parent cell.
- Chromosomes replicated during the S phase are divided in such a way as to ensure that each daughter cell receives a copy of every chromosome.
- In actively dividing animal cells, the whole process takes about one hour.
- M Phase, although a continuous process, is conventionally divided into six stages.
- The first five stages of M phase constitute mitosis: prophase, prometaphase, metaphase, anaphase and telophase.
- Cytokinesis occurs in the sixth stage.

M-Phase

- The events of the cell cycle are controlled by the cell-cycle control system.
- The core of the control system consists of various cyclin-dependent kinases (Cdks), which are activated in sequence to trigger various steps of the cycle.
- The Cdks are activated by the binding of cyclin regulatory proteins, as well as by phosphorylation and dephosphorylation of the kinase.
- They are inactivated by various Cdk inhibitory proteins (CKIs) and by the degradation of the cyclin subunits at specific stages of the cycle.
- The M-phase Cdk (M-Cdk) triggers a cascade of protein phosphorylation that initiates M phase.
- The chromosomes condense, the nuclear envelope breaks down, the endoplasmic reticulum and Golgi apparatus reorganize, the cell loosens its adhesions both to other cells and to the extracellular matrix, and the cytoskeleton radically reorganizes to bring about the highly ordered movements that will segregate the replicated chromosomes and divide the cell in two.
- Targetted protein degradation by the anaphase-promoting complex (APC) has an equally important regulatory role in mitosis.
- It initiates the separation and segregation of the replicated chromosomes, and it inactivates M-Cdk at the end of mitosis.
- Mitosis, although a continuous process, is conventionally divided into five stages: prophase, prometaphase, metaphase, anaphase and telophase.


interphase
G1 phase
S phase
G2 phase
M phase
G1 phase
nucleus
cytoplasm
chromosome replication
MITOSIS
prophase
prometaphase
metaphase
anaphase
telophase
CYTOKINESIS

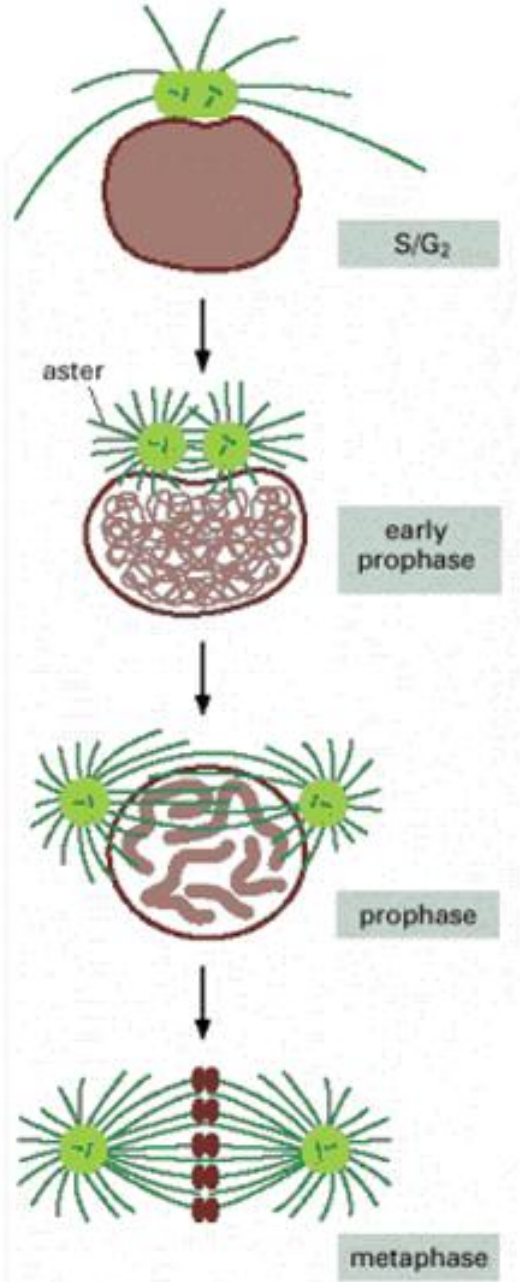
Interphase

- Interphase is the process through which a cell must go before mitosis, meiosis, and cytokinesis. Interphase consists of three main phases: G_1, S, and G_2.
- G_1 is a time of growth for the cell where specialized cellular functions occur in order to prepare the cell for DNA replication.
- In S phase, the chromosomes are replicated in order for the genetic content to be maintained.
- When the chromosomes are duplicated in S phase, the two copies of each replicated chromosome remain tightly bound together as identical sister chromatids.
- The sister chromatids are glued together by multisubunit protein complexes called cohesins, which are deposited along the length of each sister chromatid as the DNA is replicated.
- This cohesion between sister chromatids is crucial to the chromosome segregation process and is broken only late in mitosis (at the start of anaphase) to allow the sisters to be pulled apart.
- During G_2, the cell undergoes the final stages of growth before it enters the M phase, where spindles are synthesized.

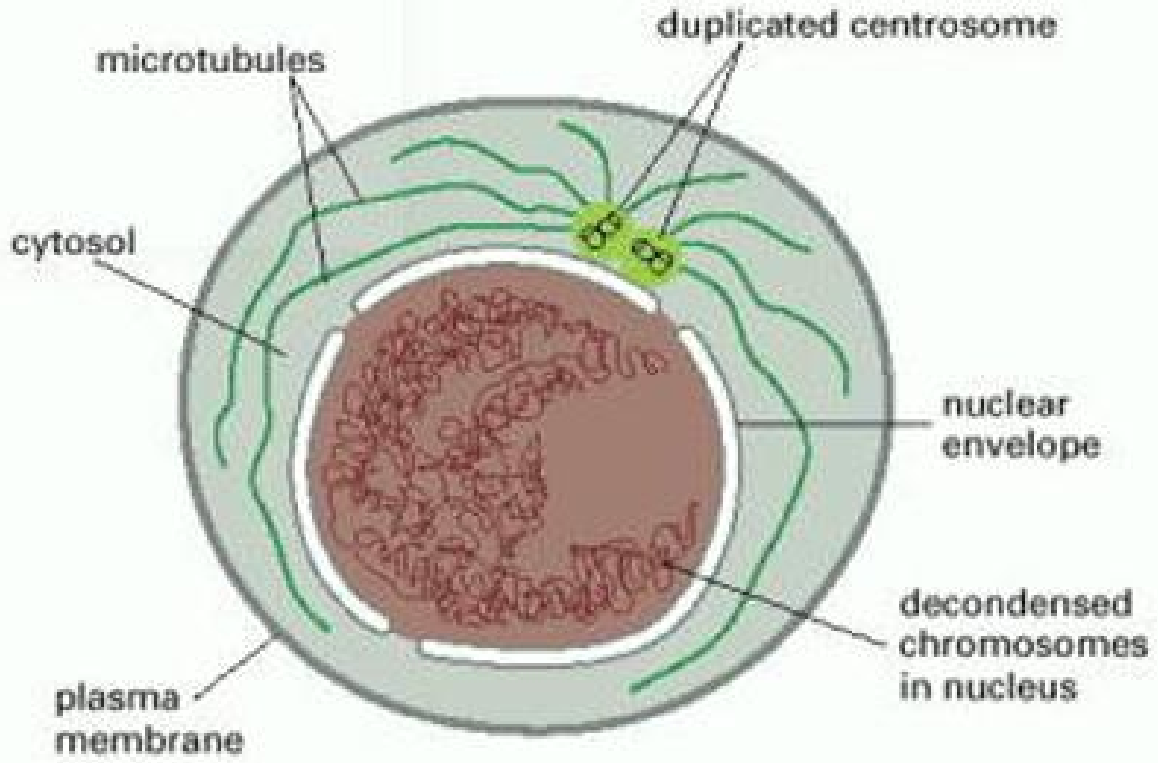
…Interphase

- The centrosome is duplicated during interphase to help initiate the formation of the two poles of the mitotic spindle and to supply each daughter cell with its own centrosome.
- During interphase, the centrosome matrix nucleates a cytoplasmic array of microtubules, with their fast-growing plus ends projecting outward toward the cell perimeter and their minus ends associated with the centrosome.
- During interphase of each animal cell cycle, the centrioles and other components of the centrosome are duplicated but remain together as a single complex on one side of the nucleus.
- As mitosis begins, this complex splits in two, and each centriole pair becomes part of a separate microtubule organizing center that nucleates a radial array of microtubules called an aster.
- The M phase can be either mitosis or meiosis depending on the type of cell.
- Germ cells, or gametes, undergo meiosis, while somatic cells will undergo mitosis.

The centrosome cycle: Centriole duplication begins in G1 and is completed by G2.



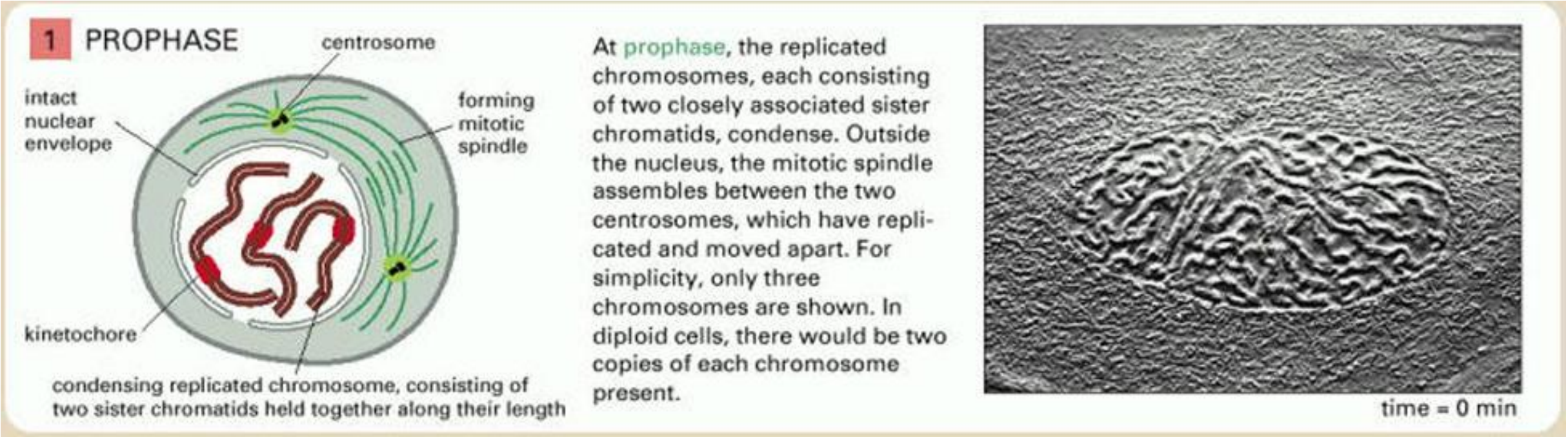
INTERPHASE



During interphase, the cell increases in size. The DNA of the chromosomes is replicated, and the centrosome is duplicated.

Prophase

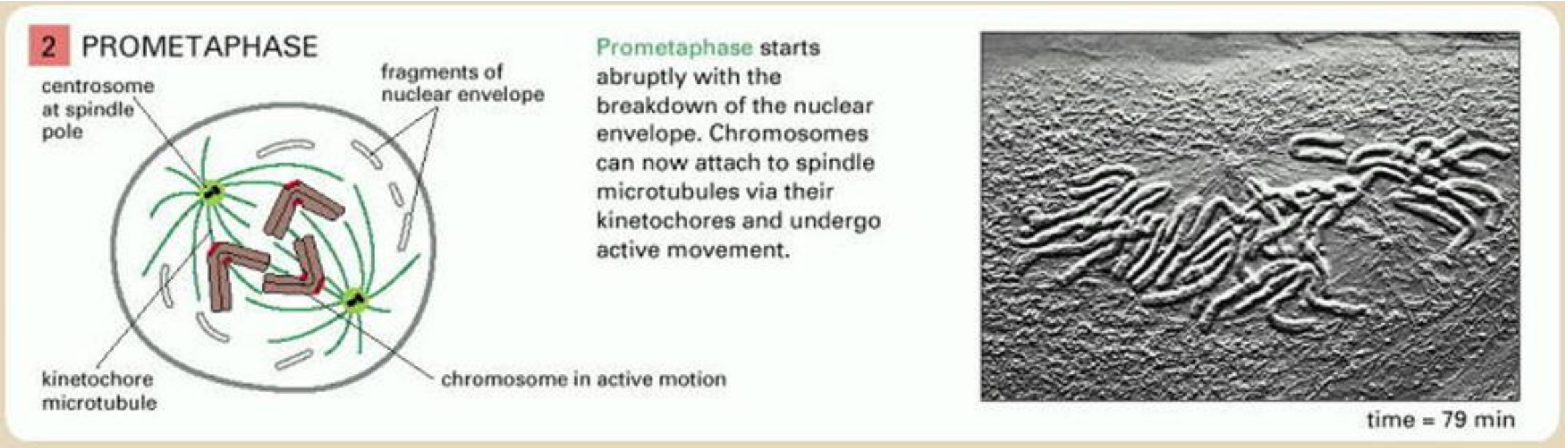
- The first readily visible sign that a cell is about to enter M phase is the progressive compaction of the replicated chromosomes, which become visible as threadlike structures a process called chromosome condensation.
- Proteins called **condensins** do the work of chromosome condensation.
- Activated M-Cdk phosphorylates some of the condensin subunits, triggering the assembly of condensin complexes on DNA and, thereby, the progressive condensation of the chromosomes.
- The two asters move to opposite sides of the nucleus to initiate the formation of the two poles of the mitotic spindle.

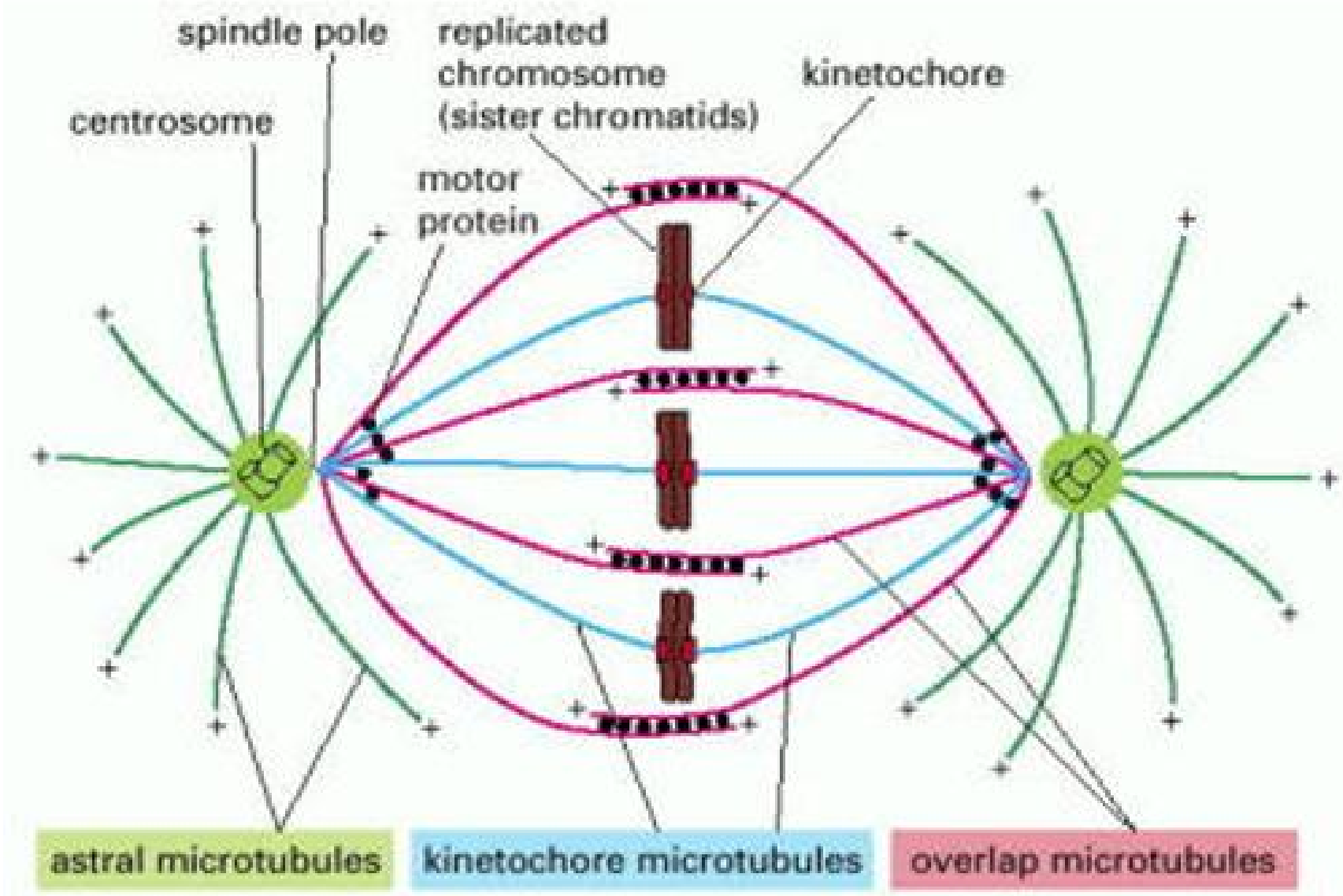


Prometaphase

- The nuclear envelope breaks down (at prometaphase), and the spindle captures the chromosomes.
- The breakdown is triggered when M-Cdk directly phosphorylates the nuclear lamina that underlies the nuclear envelope.
- The disassembly of the nuclear envelope allows the microtubules access to the condensed chromosomes for the first time.
- Now, the assembly of a mature mitotic spindle can begin and they eventually end up attached end-on (through plus end of microtubule) at the kinetochore, that assembles onto the highly condensed DNA at the centromere.
- Both the assembly and the function of the mitotic spindle depend on microtubule-dependent motor proteins.
- These proteins belong to two families the kinesin-related proteins, which usually move toward the plus end of microtubules, and the dyneins, which move toward the minus end.
- Three classes of spindle microtubules can be distinguished in mitotic animal cells.
    - Astral microtubules radiate in all directions from the centrosomes and are thought to contribute to the forces that separate the poles. They also act as "handles" for orienting and positioning the spindle in the cell.
    - Kinetochore microtubules attach end-on to the kinetochore, which forms at the centromere of each duplicated chromosome. They serve to attach the chromosomes to the spindle.
    - Overlap microtubules interdigitate at the equator of the spindle and are responsible for the symmetrical, bipolar shape of the spindle.
- All three classes of microtubules have their plus ends projecting away from their centrosome.

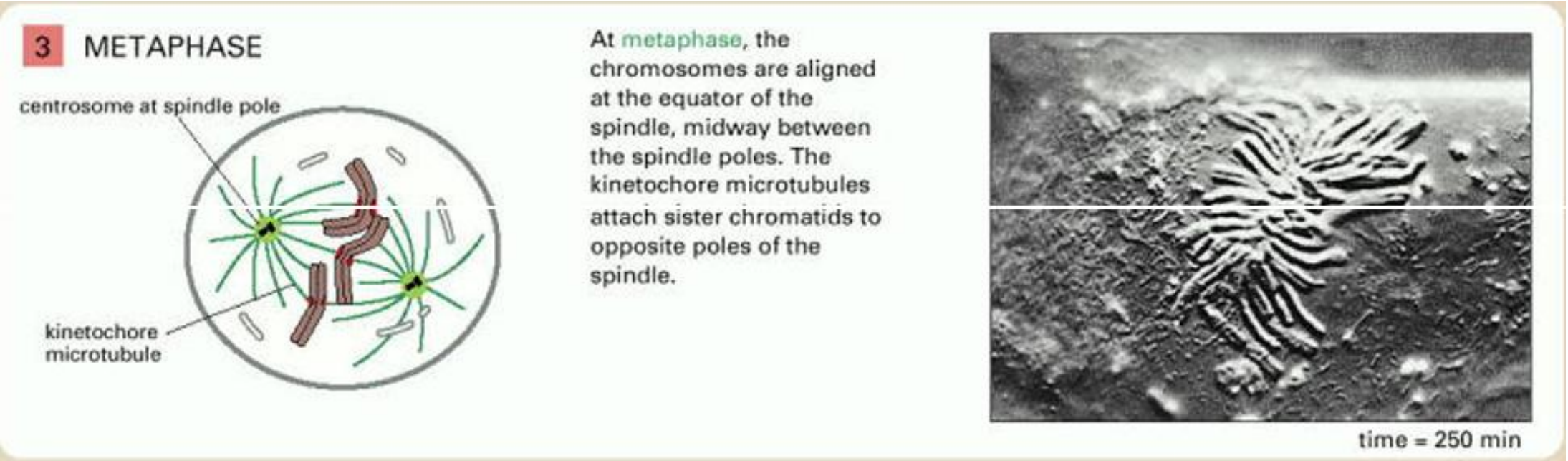
- Microtubules growing from the opposite spindle pole attach to the kinetochore on the opposite side of the chromosome, forming a bipolar attachment
- Then begins a truly mesmerizing stage of mitosis.




spindle pole
centrosome
replicated
chromosome
(sister chromatids)
kinetochore
motor
protein
astral microtubules
kinetochore microtubules
overlap microtubules

Metaphase

- First, the chromosomes are tugged back and forth, eventually assuming a position equidistant between the two spindle poles, a position called the metaphase plate.
- One of the most striking aspects of metaphase in vertebrate cells is the continuous oscillatory movement of the chromosomes at the metaphase plate.
- Seen to switch between two states a poleward (P) state, which is a minus-end-directed pulling movement, and an away-from-the-pole (AP) state, which is a plus-end-directed movement.
- Kinetochores are thought to pull the chromosomes toward the poles, while an astral ejection force is thought to push the chromosomes away from the poles, toward the spindle equator

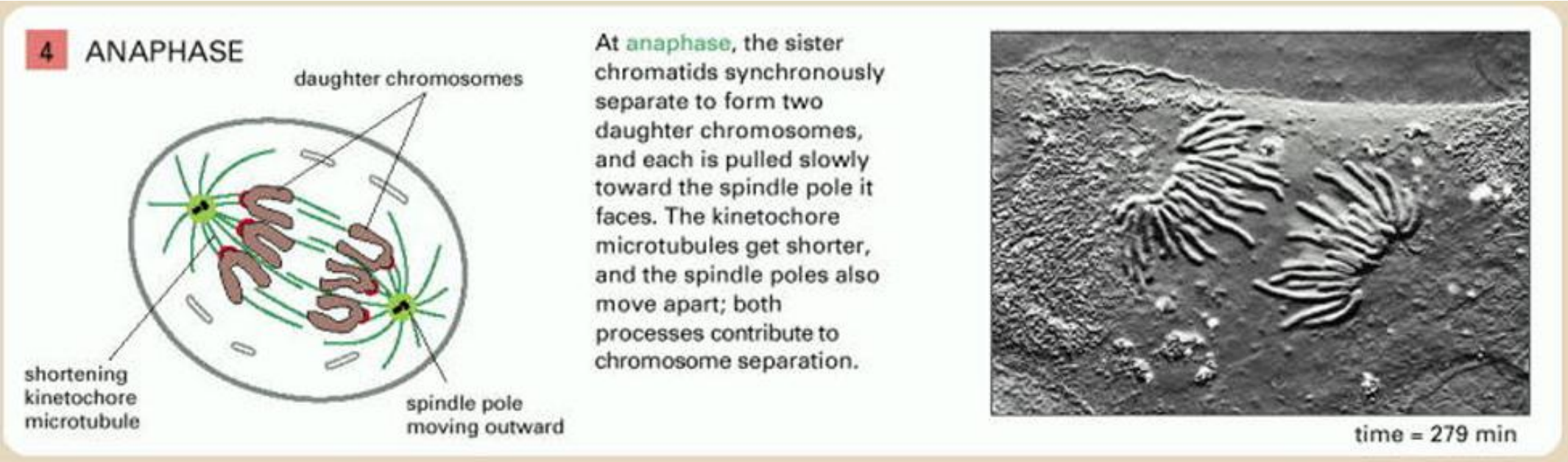


…Metaphase

- In cells without centrosomes, the chromosomes direct the assembly of a functional bipolar spindle.
- This property of the chromosomes seems to depend on a guanine-nucleotide exchange factor (GEF) that is bound to chromatin; it stimulates a small GTPase in the cytosol called Ran, inducing Ran to bind GTP in place of GDP.
- The activated Ran GTP, which is also involved in nuclear transport, releases microtubule-stabilizing proteins from protein complexes in the cytosol, thereby stimulating the local nucleation of microtubules around chromosomes.

Anaphase

- Mitotic cells usually spend about half of M phase in metaphase, with the chromosomes aligned on the metaphase plate, jostling about, awaiting the signal that induces sister chromatids to separate to begin anaphase.
- The spindle-attachment checkpoint monitors the attachment of the chromosomes to the mitotic spindle.
- It is thought to detect either unattached kinetochores or kinetochores that are not under the tension that results from bipolar attachment.
- In either case, unattached kinetochores emit a signal that delays anaphase until they all are properly attached to the spindle.

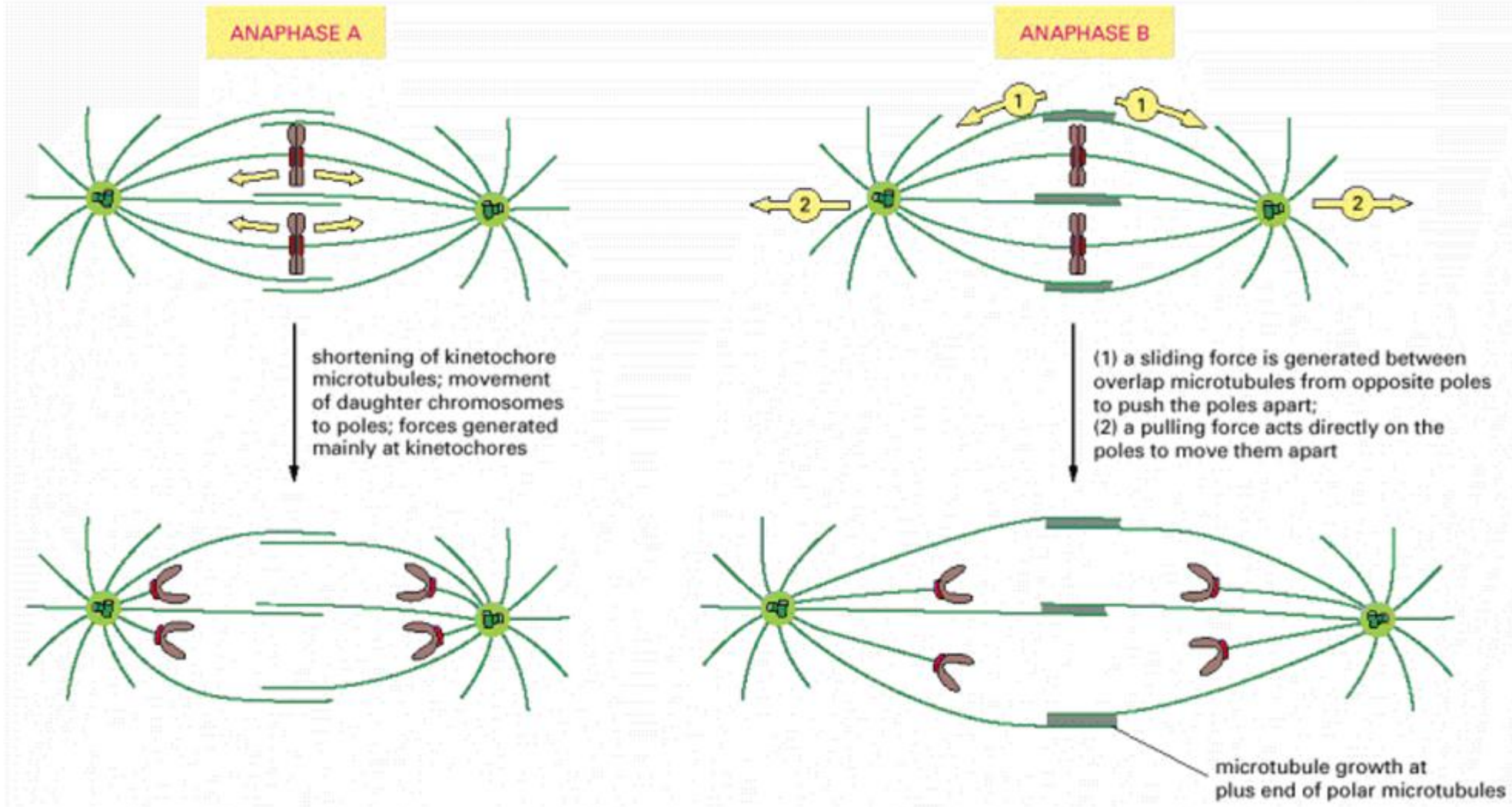


…Anaphase

- The metaphase-to-anaphase transition is triggered by the activation of the anaphase promoting complex (APC).
- Once this proteolytic complex is activated, it has at least two crucial functions:
  - (1) it cleaves and inactivates the M-phase cyclin (M-cyclin), thereby inactivating M-Cdk; and
  - (2) it cleaves an inhibitory protein (securin), thereby activating a protease called separase.
- Separase then cleaves a subunit in the cohesin complex to unglue the sister chromatids.
- The sisters immediately separate and are now called daughter chromosomes and move to opposite poles.

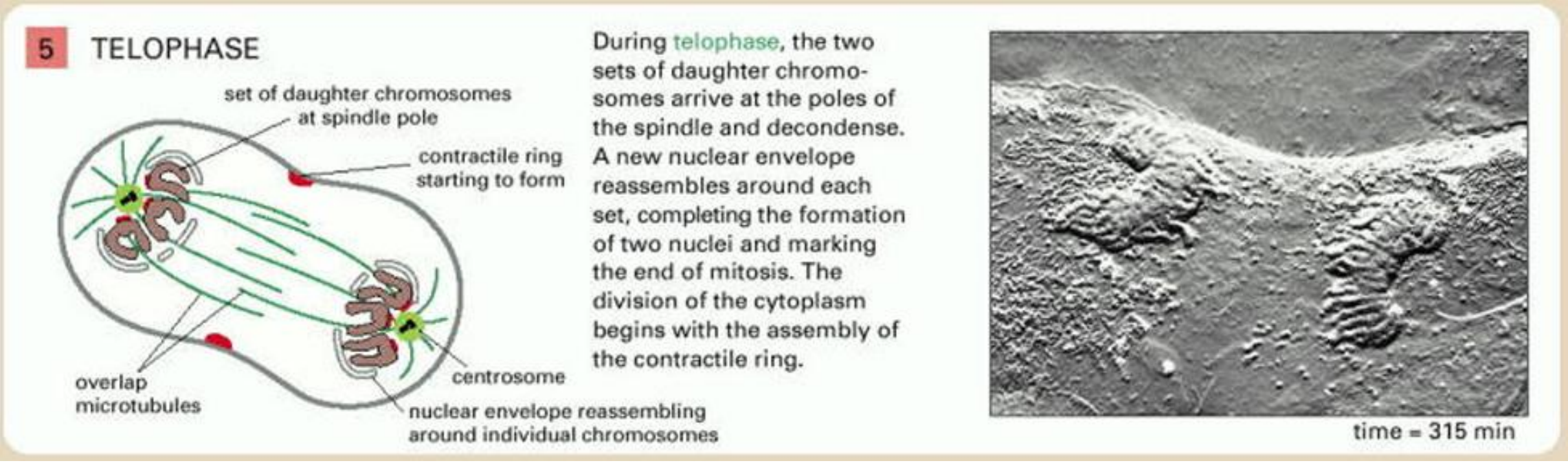
…Anaphase

- The chromosomes move by two independent and overlapping processes.
- The first, referred to as anaphase A, is the initial poleward movement of the chromosomes.
- It is accompanied by shortening of the kinetochore microtubules at their attachment to the chromosome.
- The second process, referred to as anaphase B, is the separation of the poles themselves, which begins after the sister chromatids have separated and the daughter chromosomes have moved some distance apart.


ANAPHASE A
ANAPHASE B
shortening of kinetochore microtubules; movement of daughter chromosomes to poles; forces generated mainly at kinetochores
(1) a sliding force is generated between overlap microtubules from opposite poles to push the poles apart;
(2) a pulling force acts directly on the poles to move them apart
1
1
2
2
microtubule growth at plus end of polar microtubules

Telophase

- By the end of anaphase, the daughter chromosomes have separated into two equal groups at opposite ends of the cell and have begun to decondense.
- In telophase, the final stage of mitosis, a nuclear envelope reassembles around each group of chromosomes to form the two daughter interphase nuclei.

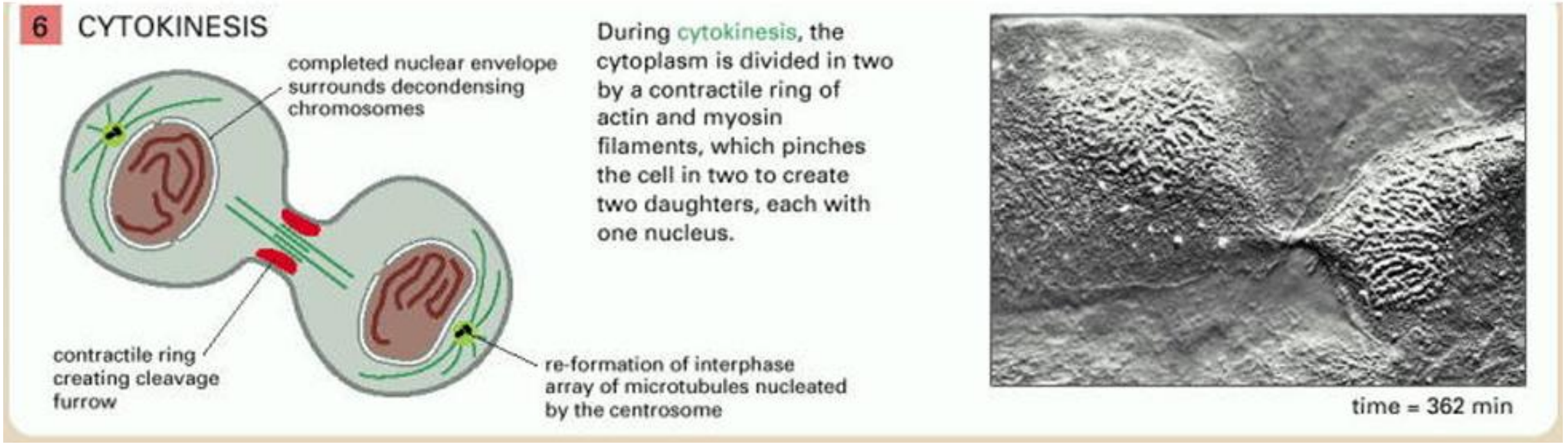


…Telophase

- Initially, the fused membrane fragments partly enclose clusters of chromosomes; the fragments then coalesce to re-form the complete nuclear envelope.
- During this process, the nuclear pore complexes are incorporated into the envelope, and the dephosphorylated lamins reassociate to form the nuclear lamina.
- The nuclear envelope once again becomes continuous with the extensive membrane sheets of the endoplasmic reticulum.
- Once the nuclear envelope has re-formed, the pore complexes pump in nuclear proteins, the nucleus expands, and the condensed mitotic chromosomes decondense into their interphase state, thereby allowing gene transcription to resume.
- A new nucleus has been created, and mitosis is complete.

Cytokinesis

- The cell cycle culminates in the division of the cytoplasm by cytokinesis.
- In a typical cell, cytokinesis accompanies every mitosis, although some cells undergo mitosis without cytokinesis and become multinucleate.
- Cytokinesis begins in anaphase and ends in telophase, reaching completion as the next interphase begins.



…Cytokinesis

- The first visible change of cytokinesis in an animal cell is the sudden appearance of a pucker, or cleavage furrow, on the cell surface.
- The furrow rapidly deepens and spreads around the cell until it completely divides the cell in two.
- In animal cells and many unicellular eucaryotes, the structure that accomplishes cytokinesis is the contractile ring a dynamic assembly composed of actin filaments, myosin II filaments, and many structural and regulatory proteins.
- The ring assembles just beneath the plasma membrane and contracts to constrict the cell into two.
- At the same time, new membrane is inserted into the plasma membrane adjacent to the contractile ring by the fusion of intracellular vesicles.
- This addition of membrane is required to compensate for the increase in surface area that accompanies cytoplasmic division.
- The mitotic spindle in animal cells not only separates the daughter chromosomes, it also specifies the location of the contractile ring, and thereby the plane of cell division.
- The contractile ring invariably forms in the plane of the metaphase plate, at right angles to the long axis of the mitotic spindle, thereby ensuring that division occurs between the two sets of separated chromosomes.

…Cytokinesis

- Most higher-plant cells are enclosed by a semirigid cell wall, and their mechanism of cytokinesis is different from that just described for animal cells.
- Rather than a contractile ring dividing the cytoplasm from the outside in, the cytoplasm of the plant cell is partitioned from the inside out by the construction of a new cell wall, called the cell plate, between the two daughter nuclei.
- The assembly of the cell plate begins in late anaphase and is guided by a structure called the phragmoplast, which contains the remaining overlap microtubules of the mitotic spindle that interdigitate at their growing plus ends.
- Small vesicles, largely derived from the Golgi apparatus and filled with polysaccharide and glycoproteins required for the synthesis of the new cell-wall matrix, are transported along the microtubules to the equator of the phragmoplast, apparently by the action of microtubule-dependent motor proteins.
- Here, the vesicles fuse to form a disclike, membrane-enclosed structure called the early cell plate.
- The plate expands outward by further vesicle fusion until it reaches the plasma membrane and the original cell wall and divides the cell in two.
- Later, cellulose microfibrils are laid down within the matrix of the cell plate to complete the construction of the new cell wall.